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09/904,557	07/16/2001	Takahiko Ishiguro	Q65441	6024

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EXAMINER
SHAW, AMANDA MARIE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,557	ISHIGURO ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed August 17, 2006. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claim 16 has been canceled. Claims 13 and 14 have been amended. Claims 13-15 will be addressed herein.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-15 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons set forth in the Office Action of August 17, 2006 and reiterated below. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection

In the instant case the specification does not appear to provide support for the amendment which recites the step of repeating steps A and B on a selected DNA molecule "that is different from the selected portion of (B)". The claim language

encompasses methods in which (i) a region is selected for testing and then the testing is repeated on an entirely different region (ii) and methods in which a region is selected for testing and then the testing is repeated using the same region but a different portion of that region. It is noted that the applicant points to the specification at page 5, line 23 through page 6 line 2 for support. The specification states "A seventh embodiment of the invention is a method for determining the gene expression region in an arbitrary region on a genome or the entire genome, which comprises repeatedly carrying out the method of the first to sixth inventions". Thus the specification provides support for repeating steps A and B but does not provide support for repeating on a different portion of the selected DNA molecule. Additionally the applicant points to the specification at pages 15-17 for support. Here the specification teaches that a region composed of 900 base pairs was divided into five specific regions each having 180 base pairs and that primer and probe sets were made for each region. However the specification does not provide support for selecting a region for testing and then repeating the testing using the same region but a different portion of that region.

RESPONSE TO ARGUMENTS

3. In the response filed August 17, 2006, Applicants traversed the new matter rejection. Applicants state that the specification does provide support for step C (repeating A and B on at least one selected portion of said selected DNA molecule that is different from the selected portion of B).

This argument has been fully considered but is not persuasive. The applicants argue that the claims recite methods for determining whether a selected DNA molecule encodes a gene expression region therefore the claims are directed to selecting a particular DNA molecule to be assayed. It is noted that there are no active process steps in which a DNA molecule is selected. The claims are further directed to screening for an RNA transcripts that corresponds to a particular portion of the DNA molecule. Finally as recited in Step C, steps A and B are repeated on at least one selected portion of said selected DNA molecule that is different from the selected portion of B. The applicants assert that for example if there was a nucleic acid 100 bp long and nucleotides 200-300 were selected in step B then in step C any other portion other than nucleotides 200-300 could be selected. However the claims as written do not support this assertion. The claims still encompass methods in which (i) a region is selected for testing and then the testing is repeated on an entirely different region (for example nucleotides 200-300 might be the first region and nucleotides 400-500 might be the second region) (ii) and methods in which a region is selected for testing and then the testing is repeated using the same region but a different portion of that region (for example nucleotides 200-300 might be the first region and nucleotides 200-220 might be the second region, in this case the region comprising nucleotides 200-220 is different with respect to the region comprising nucleotides 200-300). It is noted that the applicant points to the specification at page 5, line 23 through page 6 line 2 for support. The specification states "A seventh embodiment of the invention is a method for determining the gene expression region in an arbitrary region on a genome or the entire genome,

which comprises repeatedly carrying out the method of the first to sixth inventions". Thus the specification provides support for repeating steps A and B but does not provide support for repeating on a different portion of the selected DNA molecule. Additionally the applicant points to the specification at pages 15-17 for support. Here the specification teaches that a region composed of 900 base pairs was divided into five specific regions each having 180 base pairs and that primer and probe sets were made for each region. However the specification does not provide support for selecting a region for testing and then repeating the testing using the same region but a different portion of that region.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-15 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons set forth in the Office Action of August 17, 2006 and reiterated below.

Claims 13-15 are indefinite over the recitation of the phrase " that is different from the selected portion of (B)". It is not clear whether the method requires one to select a region to be tested and then repeat the method on an entirely different region or if the method requires one to select a region to be tested and then repeat the method using the same region but a different portion of that region. The claims are also indefinite over the recitation of "corresponding to a selected portion of". Corresponding is not an art

recognized term to describe the relationship between two nucleic acid sequences or two amino acid sequences. It is not clear as to whether a corresponding nucleic acid refers to a nucleic acid residue which is at the same position or to a nucleic acid residue which is at a nearby position or if this refers to a similar nucleic acid residue or the same nucleic acid residue at any position. Because the term "corresponding" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to nucleic acid sequences, one of skill in the art cannot determine the meets and bounds of the claimed subject matter. Additionally the phrase "a selected portion of" is considered indefinite because the phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. For example, it is unclear as to whether "a selected portion of" is any portion of any DNA sequence that has been selected by virtue of amplifying it or a portion of a specific DNA sequence.

RESPONSE TO ARGUMENTS

5. In the response filed August 17, 2006, Applicants traversed the rejections under 35 U.S.C. 112, second paragraph. This arguments have been fully considered but are not persuasive.

Applicants first argue that the phrase "that is different from the selected portion of B" is definite as written. The applicants argue that the claims clearly recite the selection of a DNA molecule, the screening of a portion of the selected DNA molecule and repeating the screening on a different portion of the selected molecule therefore it is clear that there is one selected DNA molecule and that two different portions of the selected DNA molecule are screened. However it is still not clear whether the method requires one to select a region to be tested and then repeat the method on an entirely

different region (for example if a nucleic acid sequence is 1000 bp long nucleotides 200-300 might be the first region and nucleotides 400-500 might be the second region) or if the method requires one to select a region to be tested and then repeat the method using the same region but a different portion of that region (for example nucleotides 200-300 might be the first region and nucleotides 200-220 might be the second region, in this case the region comprising nucleotides 200-220 is different with respect to the region comprising nucleotides 200-300).

Additionally applicants argue that the term "corresponding" is an art recognized term to describe the relationship between an RNA molecule and the DNA molecule that encodes it. However since the applicants have not provided any evidence to support that "corresponding" is an art recognized term, the office maintains its position that corresponding is not an art recognized term to describe the relationship between a nucleic acid sequences and an amino acid sequence. Because the term "corresponding" has not been clearly defined in the specification and because there is no art recognized definition for this term as it relates to nucleic acid and amino acid sequences, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Further applicants assert that the phrase "a selected portion of" is clear and definite as written. However this phrase in considered unclear because "a selected portion" is not clearly defined in the specification and there is no art recognized definition for this phrase.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 13 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Davey et al. (US Patent 5,409,818 Issued 1995) in view of Cao (US Patent 6582906 Filed 1999) for reasons set forth in the Office Action of August 17, 2006 and reiterated below.

As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, the method steps of the claimed invention are able to stand-alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language

of "method for determining whether a selected DNA molecule encodes a gene expression region" merely sets forth the intended use or purpose of the claimed method, but does not limit the scope of the claims.

With regard to claim 13 Davey et al. teach a method for determining whether a selected DNA molecule encodes a gene expression region which in this case is a 92 bp segment of the gag portion of the HTLV-III genome, the causative agent of AIDS (Col. 12 lines 33-35), said method comprising:

(A) obtaining RNA transcripts from an organism (ultimately HIV-1 virus, also *E.Coli*, Col. 11 line 50) which comprises said selected DNA molecule,

(B) screening said RNA transcripts for an RNA transcript corresponding to a selected portion of said selected DNA molecule, wherein the nucleotide sequence of said selected portion of said selected DNA molecule is known, to thereby determine whether said selected portion of said selected DNA molecule encodes a gene expression region such as the 92 bp segment of the gag portion of the HTLV-III genome (Col. 12 lines 33-35), wherein said screening comprised:

(i) amplifying the RNA transcripts using a first oligonucleotide primer and a second oligonucleotide primer, wherein said first primer is complementary to a sequence of at least 10 continuous nucleotides located at or near the 3'-end of said selected portion of said selected portion of said selected DNA molecule, and said second primer is homologous to a sequence of at least 10 continuous nucleotides located at or near the 5'-end of said selection portion of said selected

DNA molecule (See Figure 1 and Col. 5 lines 14-25, Col. 6 lines 19-68 for example), and

(a) forming a RNA-DNA duplex comprising one of said RNA transcripts and a complementary DNA molecule adhered thereto, said duplex is formed by synthesizing a first DNA molecule complementary to at least a portion of one of said RNA transcripts using (1) said first oligonucleotide primer to prime synthesis of said first DNA molecule, (2) RNA-dependent DNA polymerase and (3) one of said RNA transcripts as a template, to thereby form an RNA-DNA duplex as can be seen in Figure 1 and Col. 5 lines 27-35 for example.

(b) preparing a single stranded DNA molecule from said RNA-DNA duplex of (e) by hydrolyzing the RNA transcript of said RNA-DNA duplex using ribonuclease H (Col. 8 lines 20-33 for example).

(c) forming a doubled-stranded DNA molecule comprising the single-stranded DNA molecule of (f) and a complementary DNA molecule thereto, said doubled-stranded DNA molecule is formed by synthesizing a second DNA molecule complementary to at least a part of said single-stranded DNA molecule of (f) using (1) said second oligonucleotide primer to prime the synthesis of said second DNA molecule, wherein said second primer further comprises an RNA-transcriptable promoter sequence at its 5'-end, (2) DNA-dependent DNA polymerase, and (3) the single-stranded DNA molecule of (f) as a template, to thereby form a double stranded DNA molecule as can be seen in Figure 1 and further in Col. 4 lines 10-15.

(d) forming an RNA transcription product from said double-stranded DNA molecule of (g) using RNA polymerase, wherein RNA transcription is primed from the RNA-transcriptable promoter sequence(Col. 7 lines 28-47 for example).

(e) repeating steps (a) to (d) using said RNA transcription product of (d) as a template for the formation of the RNA-DNA duplex of (a)(Col. 19 claim 1(C)).

(ii) Detecting an amplification product of (i) corresponding to said selected portion of said DNA molecule, to thereby screen said RNA transcripts for an RNA transcripts for a RNA transcript that corresponds to said selected portion of said selected DNA molecule via the incorporation of a labeled precursor into the amplification process (Col. 6 lines 4-6 and Col. 8 lines 47-67 for example).

(C) repeating (A) and (B) on at least one other selected portion of said selected DNA molecule(Col. 3 lines 26-58, where the reference teaches that a "plurality of copies of the RNA sequence of the first template from the third template" can be synthesized).

Davey et al does not teach repeating (A) and (B) on at least one other selected portion of said selected DNA molecule that is different from the selected portion of (B).

However Cao teaches method used to analyze gene expression in which the method steps are repeated using a different portion of the selected DNA molecule. Specifically Cao et al teaches a method for amplification of a population of nucleic acids comprising; (i) synthesizing a single-stranded DNA population from said population of RNA; (ii) separating the DNA from the DNA/RNA hybrid using heat or an enzyme

treatment, (iii) fragmenting the single-stranded cDNA to produce a fragmented single-stranded cDNA population; (iv)synthesizing double-stranded DNA from the fragmented single-stranded cDNA population; (v) and producing multiple copies of sense RNA from said double-stranded DNA (Column 6, Claim 1). Cao also teaches that methods of the present invention are repeated once or multiple times(Column 3). As a result each time the method is repeated the starting population of RNA is different because the cDNA in step (iii) is fragmented and therefore produces a population of different dsDNA sequences which encode of a population of different mRNAs.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Davey et al so as to have repeated the methods steps on different portions of RNA in order to have achieved the benefits set forth by Cao of providing a method which overcomes having to analyze long templates for gene expression which can be difficult and less efficient due to interference from secondary and tertiary structure in the template.

Response to Arguments:

7. In the response filed August 17, 2006, Applicants traversed this rejection by stating that neither the Davey et al or the Cao et al references teach the repetition step. Additionally applicants argue that there is no motivation to combine the teachings of Davey et al and Cao et al.

This argument has been fully considered and has not been found persuasive because while Davey does not teach the concept of repeating the method on a different RNA region, Cao has been cited as teaching methods in which the method is repeated on multiple regions of an RNA molecule. In the instant case since the cDNA is fragmented, each fragment is being interpreted as a different region. Accordingly, in view of the teachings of Cao, it would have been obvious to modify method of Davey so as to have repeated the methods steps on different portions of RNA in order to have achieved the benefits set forth by Cao of providing a method which overcomes having to analyze long templates for gene expression which can be difficult and less efficient due to interference from secondary and tertiary structure in the template.

8. Claims 14 and 15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Davey et al. (US Patent 5,409,818 Issued 1995) in view of Cao (US Patent 6582906 Filed 1999) and in further view of Wittwer et al. (US Patent 6,503,720 B2 Filed 2001) for reasons set forth in the Office Action of August 17, 2006 and reiterated below.

The teachings of Davey et al and Cao et al are presented above in paragraph 6.

The combined references do not teach that the amplification product is detected using an oligonucleotide probe that is labeled with an intercalating fluorescence dye and with respect to claim 15 an intercalating fluorescence dye that has a differential fluorescence characteristic depending on whether said probe exists in an unbound single-stranded state or in a bound duplex with said amplification product.

However, Wittwer et al. (US Patent 6,503,720 B2) teach such an intercalating probe in their teaching of amplification by PCR and subsequent detection with SYBR green in Example 2, Col. 9-10 and further teach an intercalating fluorescence dye that has a differential fluorescence characteristic depending on whether said probe exists in an unbound single-stranded state or in a bound duplex with said amplification product in Col. 7 lines 6-19 for example when they assert that using their Taq Man principle detects an amplification product, which is labeled with a fluorescent entity, the fluorescence emission of which is quenched by a second label in its un-hybridized form and upon its hybridization to its target sequence and following digestion with a DNA polymerase having a 5'-3' exonuclease activity, lacks quencher and therefore fluoresces in its hybridized state as compared to its un-hybridized form. In addition, in Col. 4 lines 7-10, Wittwer specifically teaches that "within the scope of the invention, are different methods for amplifying nucleic acids, for example NASBA (WO 91102814)" which applicant themselves teach in their specification on page 11 line 6 and further in their examples as an embodied method of RNA amplification.

Therefore, It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Davey et al and Cao et al with the use of SYBR Green, intercalating based fluorescent probes of Wittwer et al. for the expected benefit derived from the Wittwer et al. probe that allows for the concentration of an amplifiable or replicable analyte being determined without correction for different fluorescent backgrounds (Col. 2 lines 22-24) and further "provides such an independence of absolute signal level for systems wherein multiple fluorescent signals

being detected through multiple channels with different window ranges may be compared"(Col. 2 lines 30-34). Furthermore, the motivation to combine the references existed since Davey's 3SR method of RNA amplification (also know as NASBA) was taught by Wittwer et al. to be "within the scope of the invention" as it is a "different method for amplifying nucleic acids, for example NASBA (WO 91102814)" as taught by Wittwer et al. in Col. 4 lines 7-10.

Response to Arguments:

9. In the response filed August 17, 2006, Applicants traversed this rejection by stating that Wittwer et al does not provide the missing step of Davey et al and Cao et al and does not provide motivation to combine the cited publications.

This argument has been fully considered and has not been found persuasive because Wittwer does in fact teach the detection of amplified product using an oligonucleotide probe labeled with an intercalating fluorescence dye. One would have been motivated to combine the references because the probes of Wittwer allow for the concentration of an amplifiable or replicable analyte to be determined without correction for different fluorescent background, independently from a user defined log phase and a user defined threshold level, and wherein at the same time the determined concentration is independent of the absolute level of signal which is generated in the plateau phase of the reaction. Moreover, such an independence of absolute signal level is also advantageous for systems, wherein multiple fluorescent signals being detected through multiple channels with different window ranges may be compared (Column 2).

Conclusion

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634